



# Systemic and targeted therapies for pancreatic ductal adenocarcinoma

Motaz Qadan<sup>1</sup>, David P. Ryan<sup>2</sup>, Theodore S. Hong<sup>3</sup>

<sup>1</sup>Department of Surgery, <sup>2</sup>Department of Medicine, <sup>3</sup>Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

*Contributions:* (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Motaz Qadan, MD, PhD. Department of Surgery, Massachusetts General Hospital, Boston, MA, USA.

Email: mqadan@mgh.harvard.edu.

**Abstract:** Pancreatic ductal adenocarcinoma (PDAC) remains among the most lethal cancers due to late presentation, early systemic metastases, and general resistance to modern systemic therapies. Defining features of PDAC include a high rate of KRAS mutation with a significant propensity for both local invasion and distant metastases. Precursor lesions for PDAC include pancreatic intraepithelial neoplasia 1, 2, and 3 (low, intermediate, and high-grade, respectively), as mutational burden increases with increasing grade. Additional mutations, such as CDKN2A, p53, and SMAD4 are increasingly found in higher grade and more advanced lesions. Approximately 70% of PDAC tumors are found in the head and uncinate process, and 30% in the neck, body, and tail. Workup of a pancreatic mass includes laboratory testing including CEA and CA 19-9, and high-resolution cross-sectional imaging. Endoscopic ultrasound (EUS), with or without endoscopic retrograde cholangiopancreatography (ERCP) are used to visualize the tumor, obtain fine-needle aspirate (FNA) or core biopsies, and place a biliary stent if needed. Approximately 15–20% of patients with PDAC present with resectable disease, which conventionally includes disease without involvement of critical vascular structures, or venous abutment less than 180 degrees, and are candidates for surgical intervention. Additional involvement of adjacent vascular structures constitutes the more advanced entities, including borderline resectable and locally advanced unresectable disease. In this review, we discuss recent advances in the treatment of localized PDAC, including upfront resectable, and locally advanced, tumors, with a focus on evidence-based, multimodal, strategies in the treatment of this disease.

**Keywords:** Pancreatic ductal adenocarcinoma (PDAC); upfront resectable; borderline resectable; locally advanced

Received: 04 May 2020; Accepted: 05 August 2020; Published: 25 August 2020.

doi: 10.21037/apc-2020-pda-06

**View this article at:** <http://dx.doi.org/10.21037/apc-2020-pda-06>

## Introduction and epidemiology

Pancreatic ductal adenocarcinoma (PDAC) remains among the most lethal cancers due to late presentation, early systemic metastases, and general resistance to modern systemic therapies. In 2019, PDAC represented 3.2% of all new cancer cases, with an estimated 56,770 new cases expected in the United States (1). Despite recent advances in management of the disease, there were approximately 45,750 deaths in 2019 (7.5% of all cancer deaths), with a

5-year survival of 9.3% among diagnosed patients.

In this review, we discuss recent advances in the treatment of localized PDAC, including upfront resectable, and locally advanced, tumors.

## Risk factors and genetics of PDAC

Defining features of PDAC include a high rate of KRAS mutation (greater than 90%) with a significant propensity

for both local invasion and distant metastases. Additional characteristic features include a desmoplastic stroma that functions as an anatomic and physiologic barrier. As a result, the tumor microenvironment results in poor vascularity, hypoxia, and evasion of host immunity. Precursor lesions for PDAC include pancreatic intraepithelial neoplasia 1, 2, and 3 (low, intermediate, and high-grade, respectively), as mutational burden increases with increasing grade. While KRAS mutations are detectable in early PanIN, additional mutations, such as CDKN2A, p53, and SMAD4 are increasingly found in higher grade and more advanced lesions. Similarly, early PanIN lesions are frequently detected in autopsy series of pancreatic specimens. However, intermediate and high-grade PanIN are more closely associated with PDAC tumors from a geographic perspective, and in patients with familial predisposition for developing PDAC. Interestingly, SMAD4 inactivation is highly associated with metastatic disease and shortened survival in patients with PDAC (2).

### Clinical presentation

Approximately 70% of PDAC tumors exist to the right of the portal vein and SMA complex, and 30% to the left, which are anatomically representative of the right and left pancreas in terms of surgical resection strategies (Whipple pancreaticoduodenectomy *vs.* distal or subtotal pancreatectomy, respectively).

Symptoms of PDAC closely mirror location, with right-sided tumors representing overall a slightly more favorable outlook due to early symptom manifestation, including jaundice, pruritus, pale stools, dark urine, and gastric outlet obstruction (3). Left-sided tumors, on the other hand, are largely asymptomatic, and are more likely to present late with metastases and/or local invasion including multivisceral (stomach, spleen, left liver, and colon) or vascular involvement. Both right and left-sided tumors may present with constitutional symptoms including pain, and more generalized weight-loss, cachexia, and weakness, which may be related to neural invasion and systemic cytokine alterations, respectively. Recent onset diabetes is an interesting development that may be related to an underlying occult pancreatic malignancy and associated with worse cancer outcomes, although not reliable enough to warrant routine pancreatic screening at this time (4).

Once a mass is detected on initial work up of suspicious signs and symptoms, often by abdominal ultrasound as the first modality, 'pancreatic protocol' computed tomography

(CT) scan is sought. This specialized scan includes use of iodinated intravenous contrast that is utilized to provide distinct and well-timed phases including precontrast, early and late arterial phases, portal venous phases, and delayed washout phases. In addition, limited oral water contrast distends the upper gastrointestinal tract while maintaining bowel translucency. Finally, thin axial cuts (1.0–2.0 mm) are provided with excellent resolution for evaluation of tumor extent, hepatic arterial anatomy, and vascular involvement. Laboratory studies should include tumor markers such as CEA and CA 19-9. Although these markers lack sensitivity, elevated markers are useful for surveillance during neoadjuvant systemic therapy and following resection to monitor for disease recurrence. Finally, endoscopic ultrasound (EUS) with or without endoscopic retrograde cholangiopancreatography (ERCP) are used to visualize the tumor, obtain fine-needle aspirate (FNA) or core biopsies, and place a biliary stent in the event of jaundice if surgical resection is not imminently planned. General surgical guidelines for placement of biliary decompression include replaced hepatic arterial anatomy (in the event hepatic vessels need to be sacrificed), acute renal failure, logistical issues associated with timing of surgical resection, need for neoadjuvant therapy, and arbitrary values of bilirubin greater than 15–20. Stent placement is associated with increased infectious complications when compared with upfront resection based on randomized controlled trial data (5). Staging to rule out distant metastatic disease is completed with a CT scan of the chest. The utility of positron emission tomography (PET) imaging and MRI beyond a high-quality pancreas protocol CT vary according to institutional protocol and may have benefit in additional staging of specific findings detected on the initial CT scan (e.g., characterization of liver lesions), albeit with an increased risk of false positive results (6).

In the event that distant metastases have already developed, the disease is no longer considered localized, and unlikely amenable to curative therapy. Localized treatment modalities such as surgery and/or radiation therapy are thereby excluded.

### Definitions of localized disease

Following completion of the pancreas protocol CT scan, a careful evaluation of the tumor can be made with respect to the vascular structures of significance in the region (7). Following confirmation of absence of metastatic disease, arterial vessels including the celiac axis, common hepatic

artery, replaced and accessory hepatic vessels, superior mesenteric artery and, less importantly, the splenic artery are evaluated. From a venous perspective, vessels including the portal vein, superior mesenteric vein, first jejunal branch and distal mesenteric venous branches, and the splenic vein are evaluated. Traditionally, involvement is described as abutment (less than 360-degree involvement and further categorized into less than or greater than 180 degrees involvement) or encasement, which occurs with or without occlusion (360-degree involvement). Invasion, while rare, is possible. Definitions based on degree of abutment or encasement now exist and are used traditionally to define tumors as upfront resectable or locally advanced, with the latter category divided into the more distinct entities of borderline resectable *vs.* locally advanced unresectable disease (8). In general, upfront resectable disease refers to less than 180 degrees of venous abutment.

### Treatment of upfront resectable disease

Traditionally, the treatment of upfront resectable disease, which conventionally includes disease without involvement of critical vascular structures, or venous abutment less than 180 degrees, has been surgical resection. Strictly speaking, surgical resection provides the only path towards cure. Approximately 15–20% of patients with PDAC present with resectable disease and are candidates for surgical intervention (9).

In the traditional surgery-first approach, a substantial proportion of patients resected are ultimately found to have a microscopically positive margin on final pathology, including the pancreatic neck margin, retroperitoneal margin, and/or SMA margin (10). Whether or not a microscopic positive margin at the pancreatic neck impacts overall survival remains unknown, with various series reporting conflicting results (11,12). However, complete extirpation of upfront resectable disease remains an important objective.

As discussed above, a Whipple pancreaticoduodenectomy is the operation of choice for right-sided disease, as defined by the SMV/SMA complex. Originally devised by Allen Oldfather Whipple as a two-stage operation in the 1940's, the operation has routinely been carried out as a single stage operation with relatively slight evolution in technique beyond improved operating times, reduced morbidity and mortality, and lower estimated blood loss over the years. Despite multiple trials investigating multiple variations in technique, little difference has been detected in technical

variations, including pylorus resection *vs.* pylorus sparing operations, extended *vs.* conventional lymphadenectomies, pancreaticojejunostomy *vs.* pancreaticogastrostomy, and choice of surgical incision. For tumors located in the tail or body, the choice of operation includes a distal, or subtotal, pancreatectomy (extending to the SMV). Splenectomy is routinely included for PDAC as the standard of care to incorporate draining lymph nodes, and more limited resection including enucleations or central resections are not recommended.

Recent efforts to increase minimally-invasive approaches, including laparoscopic, robotic, hand-assisted, and hybrid approaches have continued to succeed, although oncologic outcomes and return to intended oncologic therapy (RIOT) times have remained relatively stable based on surgical approach alone (13). Early dissemination of PDAC in the form of systemic micrometastases, which reflects aggressive tumor biology, continues to be the dominant factor impacting oncologic outcomes and survival. This concept highlights the established importance of systemic therapy in the multimodal treatment of PDAC as the dominant factor impacting survival, including choice of systemic agent, timing of delivery, and chemoresponse.

### Adjuvant therapy

The use of systemic chemotherapy, to reduce distant metastases, and radiation therapy, to prevent local failures, have been extensively investigated and utilized in recent years, given the continued failure rate (recurrence) following adequate surgical resection. Several studies to-date have confirmed the benefit of adjuvant systemic therapy with gemcitabine or fluorouracil compared with observation alone (14-19).

More recently, however, a study incorporating the use of multiagent fluorouracil, irinotecan, oxaliplatin, and leucovorin (FOLFIRINOX) in the metastatic setting demonstrated superior survival compared with single-agent adjuvant gemcitabine (20). Incidentally, patients were only randomized following surgical resection, thereby selectively including healthier patients who would be able to tolerate aggressive systemic therapy. Consequently, patients median overall survival were superior than prior studies in PDAC, including in the gemcitabine only study arm. Nonetheless, the use of FOLFIRINOX in the adjuvant setting was thus established as the standard of care following publication of the study's impressive results. The use of gemcitabine in combination with albumin-bound paclitaxel (nab-paclitaxel),

which is largely considered equivalent to FOLFIRINOX based on the metastatic data, does not seem to be associated with similar benefit in preliminary data analysis from the APACT trial, although the combination of gemcitabine with capecitabine has been established as superior to gemcitabine monotherapy in ESPAC-4 (21,22).

While the role of chemotherapy in the adjuvant setting is well established, the benefit of radiation therapy is less clear based on two, arguably flawed, European studies that failed to demonstrate any benefit. Results from a recently completed randomized trial evaluating the role of radiation in the United States are pending (NCT01013649) (23).

### **Neoadjuvant therapy**

Given the previously described high rate of microscopic positive margins, in addition to the high frequency of node positive disease, the use of neoadjuvant therapy has been explored in an attempt to ensure negative margin resections and improve pathologic parameters of tumors following extirpation. In addition, by providing treatment upfront, the need for adjuvant therapy is avoided, which is often poorly tolerated, and frequently omitted (25–50% of patients), following major pancreatectomy (24). With added success in the use of neoadjuvant therapies such as FOLFIRINOX and gemcitabine/nab-paclitaxel in locally advanced tumors (below), the concept continues to be explored for upfront resectable disease (25). In addition, a Japanese randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 *vs.* upfront surgery for resectable pancreatic cancer (Prep-01/JSAP-05) in 269 patients who underwent resection with curative intent was recently reported (26). The benefit of neoadjuvant therapy were readily demonstrated, with a median overall survival of 36.7 months in the neoadjuvant arm *vs.* 26.6 months for upfront surgery (hazard ratio =0.72;  $P=0.015$ ). The 2-year overall survival rates were 63.7% *vs.* 53.5%, respectively. Finally, lymph node metastases were also lower in the neoadjuvant group (59.6% *vs.* 81.5%) in the press release, without any differences in operating time, bleeding events, operative technique, morbidity, or mortality.

While neoadjuvant therapy use may seem intuitive, the downside concerns include rendering resectable disease unresectable due to disease progression, systemic toxicities, or treatment-related complications (e.g., cholangitis with ERCP stent). Although no current randomized clinical data exist to support an exclusive neoadjuvant approach for resectable disease at this time, extrapolation of data

from the locally advanced cohorts with improved outcomes appear to support application of neoadjuvant therapy in the resectable setting, and has been adopted as the standard approach at many global institutions.

In terms of the choice of chemotherapy regimen (FOLFIRINOX *vs.* gemcitabine/nab-paclitaxel), current clinical practice is based on equivalence with institutional and personal preferences determining the decision of which agent combination to use, in addition to patient tolerance and side-effect profiles. In a phase II randomized clinical trial, the use of FOLFIRINOX *vs.* gemcitabine/nab-paclitaxel in patients with resectable pancreatic cancer and excellent performance status is being evaluated (NCT02562716) (27). Results are pending at this time, and the trial is currently closed for further accrual.

In the event that neoadjuvant therapy is not pursued, adjuvant therapy with FOLFIRINOX is associated with improved outcomes and provides a reasonable alternative that represents the current standard of care. The decision at many institutions between neoadjuvant *vs.* adjuvant therapies is employed on an individual basis and careful patient evaluation and wishes.

### **Treatment of borderline resectable and locally advanced unresectable disease**

Based on the successful incorporation of multiagent regimens such as FOLFIRINOX and gemcitabine/nab-paclitaxel in the treatment of metastatic PDAC, attempts to convert locally advanced tumors to surgically resectable tumors using these regimens have been successfully employed with remarkable outcomes both in the borderline and locally advanced unresectable setting. It is these findings that have provided impetus for incorporation of neoadjuvant therapy in upfront resectable disease, as described earlier.

In an early series published from the Massachusetts General Hospital evaluating the use of neoadjuvant therapy in treatment and downstaging of locally advanced PDAC, the authors evaluated the accuracy of imaging in determining resectability following neoadjuvant therapy with FOLFIRINOX (28). Among the most important findings revealed in that study was that high-resolution radiologic imaging could not reliably distinguish between treatment-related fibrosis *vs.* viable tumor. In fact, in the absence of radiologic growth, spread, and progression combined with declining CA 19-9, surgical exploration with intraoperative biopsies of suspicious unresectable tissue

(encasing vessels) was carried out. The authors were able to complete negative-margin resection in 92% of patients, despite tumors appearing as unresectable based on imaging criteria alone. Additional findings in that landmark study to the approach of locally advanced disease included longer operating times and higher estimated blood loss among locally advanced patients who received neoadjuvant therapy compared with upfront resectable patients who did not (historic control group), reflecting the increased complexity of surgery following neoadjuvant therapy. However, there was a paradoxical decrease in operative morbidity including a zero postoperative pancreatic fistula rate, as well as a decrease in node positivity, reduction in tumor size, decrease in perineural and lymphatic invasion, and an increase in negative-margin resection rates. The stark impact of neoadjuvant therapy on node and margin status was immediately apparent. Importantly, these operations were still safely carried out with an equivalent patient length of stay during index hospitalization, readmission rate, and mortality. In addition, median overall survival confirmed the benefit associated with neoadjuvant therapy, with survival in the FOLFIRINOX arms reaching 43.7 months compared with 25.1 months in historic upfront resectable patients from operation. In 16% of patients, there was less than 1 mm of residual tumor in patients' tumors. Based on these data, the role of neoadjuvant therapy, at least for locally advanced tumors, was quickly established.

In a subsequent follow up series, the same authors attempted to identify predictors of resectability in survival in patients with locally advanced disease who underwent treatment with FOLFIRINOX (29). While the survival advantage was confirmed once again compared with historic patients who underwent upfront resection for early tumors, resectability of locally advanced tumors could not be predicted based on imaging tumor size or serum CA 19-9 levels. In addition, among locally advanced patients who could undergo successful resection, median overall survival was 43.7 months, compared with 18.6 months in locally advanced patients who were not resected.

In a study of patients with borderline resectable (and upfront resectable) pancreatic adenocarcinoma, the authors of the PREOPANC trial evaluated the use of preoperative chemoradiotherapy *vs.* upfront resection in a multicenter phase III randomized controlled trial (30). Both arms of the study incorporated adjuvant systemic therapy in addition, and radiation consisted of gemcitabine-based 34 Gray administered over 15 fractions. Among 246 included patients, preoperative chemoradiotherapy

resulted in improved overall survival (17.1 *vs.* 13.5 months;  $p=0.047$ ), R0 resection rates (65% *vs.* 31%;  $P<0.001$ ), and disease-free survival (11.2 *vs.* 7.9 months;  $P=0.010$ ). The benefit of preoperative chemoradiotherapy appeared to be considerable.

In a separate study from Korea evaluating the oncological benefit of chemoradiation with gemcitabine *vs.* upfront surgery in patients with borderline resectable disease, the authors of this recent trial assigned 110 patients to either neoadjuvant chemoradiation (54 Gray external beam radiation) followed by surgery or upfront surgery followed by chemoradiation at 4 high-volume centers, with a primary endpoint of 2-year overall survival (31). In an intention-to-treat analysis, median overall survival was significantly improved in the neoadjuvant therapy group compared with upfront surgery patients (40.7% *vs.* 26.1%;  $P=0.028$ ). In addition, R0 resection rates were also statistically significantly higher (51.8% *vs.* 26.1%;  $P=0.004$ ). The study was terminated early due to the favorable results that strongly supported the neoadjuvant cohort.

Finally, in the Alliance for Clinical Trials in Oncology Trial A021101, the authors evaluated the use of preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer, and noted in this single-arm trial implemented across 14-member institutions that 15 of 22 patients (68%) underwent successful resection, of whom 12 (80%) required vascular resection and 14 (93%) underwent R0 resections (32). Two patients (13%) had complete pathologic responses and median overall survival of all patients was 21.7 months from registration.

Based on the impressive prospective findings reported above, two subsequent phase II studies performed at the Massachusetts General Hospital subsequently confirmed the benefit of the neoadjuvant strategy in both borderline resectable and locally advanced unresectable PDAC patients. The studies showed that by combining neoadjuvant FOLFIRINOX with chemoradiation, negative margin resections could be successfully attained in 65% and 61% of patients respectively (33,34). In the locally advanced study, Losartan, an angiotensin receptor blocker, was included, based on prior data in patients with Marfan's disease that confirmed the effect of the anti-hypertensive medication on disruption of normal collagen matrix (35). Additional effects of Losartan included inhibition of collagen I production by cancer-associated fibroblasts from breast cancer biopsies in a dose-dependent manner while improving intratumoral distribution of nanoparticles and nanotherapeutics (36).

An association with improved survival was subsequently confirmed with use of ace-inhibitors and angiotensin receptor blocker use in resected patients on retrospective review (37). The benefit was also confirmed on prospective evaluation. In fact, between the two prospective phase II studies, resection rates between borderline resectable and locally advanced unresectable tumors appeared comparable, despite variable and strict definitions that suddenly appeared to become academic in nature. In addition, among patients with locally advanced unresectable disease, there were three complete pathological responders and with substantially smaller tumors sizes noted among resected patients. Consequently, Losartan has now been incorporated in a phase III study to evaluate its role in combination with neoadjuvant therapy and immunotherapy in a multi-institutional study in the United States (NCT03563248) (38).

In the current era of neoadjuvant therapy in the treatment of locally advanced pancreatic cancer, additional complimentary modalities, such as intraoperative radiation therapy (IORT) and irreversible electroporation (IRE), otherwise also known as Nanoknife<sup>®</sup>, have been utilized. For successfully resected patients with close or positive margins, margin attenuation with IORT has proven to be effective. Alternatively, IORT has also been utilized for treatment consolidation in the event of persistent localized technically unresectable disease. Among 158 patients who received IORT at the Massachusetts General Hospital with locally advanced disease who underwent neoadjuvant therapy, 86 patients underwent combined surgical resection with 10 Gray IORT while 46 patients underwent IORT alone (15–20 Gray) (39). Median progression-free survival and overall survival among patients who underwent combined resection and IORT were 21.5 and 46.7 months, respectively. In patients who could not be resected and received IORT alone, median progression-free survival and overall survival were 14.7 and 23 months, respectively. Overall, complications were limited, and with the association with improved survival exhibited in the retrospective series by the authors, the use of IORT as a complimentary modality appears to be justified.

With respect to IRE in locally advanced disease, a recent single-center prospective cohort study (IMPALA) performed in consecutive patients in the Netherlands evaluated the role of resection or IRE in 93 patients following induction chemotherapy with FOLFIRINOX (40). After 3 months, 59 patients (64%) did not progress and 36 underwent exploration. In total, 14 patients were resected, and 15 patients underwent IRE. Unfortunately, 16 patients had

grade 3 or higher complications with a 90-day all-cause mortality of 11%. Median overall survival after resection, IRE, and non-progressive patients who did not undergo neither resection nor IRE were 34, 16, and 15 months, respectively. The authors concluded that there was no apparent benefit of IRE, despite “considerable morbidity”. A separate report by Martin and colleagues evaluating use of IRE in 200 locally advanced patients reported an overall median survival of 24.9 months among patients pretreated with induction chemotherapy, despite a 37% complication rate (41). The cohort included both patients who were resected (margin accentuation) and patients who were not resected in whom IRE was administered as a definitive ablative treatment modality.

## Conclusions

There is substantial variability in the treatment of localized disease in patients with pancreatic cancer, including use of neoadjuvant therapy, decisions to pursue exploration with intraoperative biopsies, imaging modalities, surrogates of chemoresponse, the need for vascular resections and reconstructions, and margin attenuation with supplemental therapies such as IORT and IRE. However, most modern regimens and treatment combinations have resulted in substantially improved survival figures with recent paradigm shifts in the approach to localized disease in patients in the treatment of pancreatic cancer.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editor (Dr. Colin Weekes) for the series “Systemic and Targeted Therapies for Pancreas Ductal Adenocarcinoma” published in *Annals of Pancreatic Cancer*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apc-2020-pda-06>). The series “Systemic and Targeted Therapies for Pancreas Ductal Adenocarcinoma” was commissioned by the editorial office without any funding or sponsorship. Dr. DPR reports other from

Acworth Pharmaceuticals, personal fees and other from MPM Capital, other from Thrive Earlier Detection, personal fees from Gritstone Oncology, personal fees from Maverick Therapeutics, personal fees from Johns Hopkins University Press, personal fees from Uptodate, personal fees from McGraw Hill, grants from SU2C, outside the submitted work. Dr. TSH reports personal fees from Synthetic biologics, personal fees from Novocure, personal fees from Merck, non-financial support from BMS, non-financial support from Ipsen, non-financial support from Tesaro, non-financial support from Astra-Zeneca, non-financial support from Taiho, outside the submitted work. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/apc-2020-pda-06

**Cite this article as:** Qadan M, Ryan DP, Hong TS. Systemic and targeted therapies for pancreatic ductal adenocarcinoma. *Ann Pancreat Cancer* 2020;3:10.